
Hand2 function in second heart field progenitors is essential for cardiogenesis.

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Public Summary:

Cardiogenesis involves the contributions of multiple types of progenitor cells, including mesoderm-derived cardiac progenitors known as the first and second heart fields. Disruption of genetic pathways regulating individual subsets of cardiac progenitors likely underlies many forms of human cardiac malformations. Hand2 is a type of transcription factor, or protein that binds to specific DNA sequences to control the flow of genetic information from DNA to mRNA. Hand2 is expressed in numerous cell lineages that contribute to the developing heart. However, mice that lack Hand2 die in utero early in their development, making it impossible to study how the functional effects of Hand2 on cardiac progenitor cells might be passed down to offspring. In this study, we knocked out Hand2 to study how the loss of Hand2 affects the development of specific cardiac cell populations at defined developmental points. We found that Hand2 expression within the mesoderm-derived second heart field progenitors was required for their survival. Loss of Hand2 at later stages of development and in restricted domains of the second heart field revealed a spectrum of cardiac anomalies resembling forms of human congenital heart disease. Molecular analyses of Hand2 mutant cells revealed several genes by which Hand2 may influence expansion of the cardiac progenitors. These findings demonstrate that Hand2 is essential for survival of second heart field progenitors and that the graded loss of Hand2 function in this cardiac progenitor pool can cause a spectrum of congenital heart malformation.

Scientific Abstract:

Cardiogenesis involves the contributions of multiple progenitor pools, including mesoderm-derived cardiac progenitors known as the first and second heart fields. Disruption of genetic pathways regulating individual subsets of cardiac progenitors likely underlies many forms of human cardiac malformations. Hand2 is a member of the basic helix loop helix (bHLH) family of transcription factors and is expressed in numerous cell lineages that contribute to the developing heart. However, the early embryonic lethality of Hand2-null mice has precluded lineage-specific study of its function in myocardial progenitors. Here, we generated and used a floxed allele of Hand2 to ablate its expression in specific cardiac cell populations at defined developmental points. We found that Hand2 expression within the mesoderm-derived second heart field progenitors was required for their survival and deletion in this domain recapitulated the complete Hand2-null phenotype. Loss of Hand2 at later stages of development and in restricted domains of the second heart field revealed a spectrum of cardiac anomalies resembling forms of human congenital heart disease. Molecular analyses of Hand2 mutant cells revealed several genes by which Hand2 may influence expansion of the cardiac progenitors. These findings demonstrate that Hand2 is essential for survival of second heart field progenitors and that the graded loss of Hand2 function in this cardiac progenitor pool can cause a spectrum of congenital heart malformation.

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